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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/659,501	09/10/2003	Ned M. Weinshenker	25732.NP	7515

20551 7590 10/03/2006

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EXAMINER	
LEWIS, PATRICK T	

ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 10/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/659,501	WEINSHENKER ET AL.	
	Examiner	Art Unit	
	Patrick T. Lewis	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 July 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 September 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's Response Dated July 10, 2006

1. Claims 1-21 are pending. An action on the merits of claims 1-21 is contained herein below.

2. The rejection of claims 1-21 under 35 U.S.C. 112, second paragraph, has been withdrawn in view of applicant's arguments dated July 10, 2006.

3. The rejection of claims 1-21 under 35 U.S.C. 103(a) is maintained for the reasons of record as set forth in the Office Action dated September 13, 2005.

Rejections of Record Set Forth in the Office Action Dated September 13, 2005

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

5. Claims 1-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Grissom et al. US 6,797,521 (Grissom), Toki et al. J. Org. Chem. (2002), Vol. 67, pages 1866-1872 (Toki), Dubowchik et al. Bioorganic & Medicinal Chemistry Letters (1998), Vol. 8, pages 3341-3346 (Dubowchik), and Habberfield et al. US 5,574,018 (Habberfield).

Claims 1-5 and 7-20 are drawn to an anti-tumor drug and cobalamin conjugate comprising a cobalamin, or a derivative or analogue thereof; a linker covalently bound to the 5'-OH moiety of cobalamin or cobalamin derivative; and an anti-tumor drug covalently bound to the linker thereby forming the conjugate. Claims 6 and 21 are

drawn to a method of treating a tumor using the instantly claimed anti-tumor drug and cobalamin conjugate.

Grissom teaches that a doxorubicin-cobalamin conjugate was synthesized as a potential chemotherapeutic compound (column 5, line 55 to column 6, line 5). Cellular uptake of the doxorubicin-cobalamin conjugate can be observed in P-388 murine leukemia cells, as well as in HCT-116 human colon tumor cells.

Grissom differs from the instantly claimed compound in that Grissom is silent on the chemical structure of the doxorubicin-cobalamin conjugate; however, the instantly claimed anti-tumor drug and cobalamin conjugate would have been obvious to one of ordinary skill in the art at the time of the invention in view of the teachings of Dubowchik, Habberfield and Toki.

Toki teaches that peptide-containing anticancer prodrugs have been developed that are activated by proteases within solid tumors (pages 1866-1867). The drugs can be appended directly to the peptide, leading to prodrugs that can either release the parent drug or a drug that contains vestiges of the bound peptide. In the latter case, the released drug may have impaired cytotoxic activity. An additional consideration for direct drug attachment to peptides is the negative influence the drug can have on the kinetics of peptide hydrolysis. To circumvent these potential shortcomings, an alternative approach for drug attachment incorporates the use of self-immolative spacers that spatially separate the drug from the site of enzymatic cleavage. The subsequent collapse of the incorporated linkers allows for the elimination of the fully active, chemically unmodified drug from the conjugate upon amid bond hydrolysis. One

of the most commonly used spacers is the bifunctional p-aminobenzyl alcohol group, which is linked to the peptide through the amine moiety, forming an amide bond. Amine-containing drugs are attached through carbamate functionalities to the benzylic hydroxyl group of the linker. The resulting prodrugs are activated upon protease-mediated cleavage, leading to a 1,6-elimination reaction that releases the unmodified drug, carbon dioxide, and remnants of the linker group.

Dubowchik teaches peptide-DOX (doxorubicin) substrates that contain a self-immolative PABC spacer that are efficiently cleaved by cathepsin B to release free DOX but are very stable in human plasma (page 3345). Cathepsin B is an attractive target for release of drugs from conjugates that are taken up by receptor-mediated endocytosis since it is ubiquitous and found in relatively high levels in mammalian lysosomes. In addition, several of these compounds release DOX on a time scale that may make them useful as prodrugs for metastatic or primary tumors that express extracellular cathepsin B.

Habberfield teaches that the gastrointestine (i.e. G.I.) is an organ of the body that functions to physically, chemically and enzymatically process and break down ingested nutrients (columns 1-3). Uptake of nutrients, or more specifically their digestive products, takes place principally in the small intestine. The intestine is lined with a mucus layer. The mucus layer acts as a barrier to macromolecules, e.g., molecules having a molecular weight of greater than 17 kilodaltons. Thus, the lining of the intestine serves as an efficient barrier to both lipophilic and hydrophilic molecules. As a consequence, the oral administration of a large, macromolecular therapeutical

compound is normally limited as to effectiveness. However, some molecules are specifically taken up in the G.I. tract as a normal function of the digestive process. Of special interest here is the biological mechanism for the uptake of vitamin B12. It has been proposed that this vitamin B12 mechanism may be utilized to transport biologically active substances such as drugs, hormones, antigenic material, and the like, from the intestinal lumen into circulatory blood by covalently couplings these substances to vitamin B12. Habberfield further teaches conjugates formed using a chemical approach involving covalently linking vitamin B12 to a therapeutic compound (protein) via the primary (5') hydroxyl group of the ribose moiety of vitamin B12. The resulting conjugates are capable of administration to mammals through various modes of delivery, preferably oral. In general, biologically active conjugates are prepared by reacting the therapeutically active compound with 5'-O-[glutaroyl]cyanocobalamin under conditions which form covalent bonds between the two. Preferably, a 5'-O-glutaroyl derivative of vitamin B12 is formed by acylation of vitamin B12 with a reactive glutaric acid derivative to selectively convert the primary hydroxyl group (5'-OH) on the □-ribose moiety to a chemically reactive carboxyl group. The vitamin B12 derivative is then preferably reacted with a functional linker and/or spacer group to form a second derivative, which in turn is reacted with the therapeutic compound to form a biologically active conjugate.

It would have been obvious to one of ordinary skill in the art to produce an anti-tumor drug and cobalamin conjugate comprising a cobalamin, or a derivative or analogue thereof; a linker covalently bound to the 5'-OH moiety of cobalamin or

cobalamin derivative; and an anti-tumor drug covalently bound to the linker thereby forming the conjugate wherein the drug is cleavable from the linker and/or the linker is cleavable from the drug by an intracellular enzyme. Although Grissom is silent on the specific attachment of the components of the doxorubicin-cobalamin conjugate, Habberfield teaches that, in general, biologically active conjugates are prepared by reacting the therapeutically active compound with 5'-O-[glutaroyl]cyanocobalamin under conditions which form covalent bonds between the two. Preferably, a 5'-O-glutaroyl derivative of vitamin B12 is formed by acylation of vitamin B12 with a reactive glutaric acid derivative to selectively convert the primary hydroxyl group (5'-OH) on the α-ribose moiety to a chemically reactive carboxyl group. The vitamin B12 derivative is then preferably reacted with a functional linker and/or spacer group to form a second derivative, which in turn is reacted with the therapeutic compound to form a biologically active conjugate.

It would have also been obvious to one of ordinary skill in the art at the time of the invention to select a linker that is cleavable by an intracellular enzyme. Toki teaches that peptide-containing anticancer prodrugs have been developed that are activated by proteases within solid tumors. The drugs can be appended directly to the peptide, leading to prodrugs that can either release the parent drug or a drug that contains vestiges of the bound peptide. In the latter case, the released drug may have impaired cytotoxic activity. An additional consideration for direct drug attachment to peptides is the negative influence the drug can have on the kinetics of peptide hydrolysis. To circumvent these potential shortcomings, an alternative approach for

drug attachment incorporates the use of self-immolative spacers that spatially separate the drug from the site of enzymatic cleavage. The subsequent collapse of the incorporated linkers allows for the elimination of the fully active, chemically unmodified drug from the conjugate upon amid bond hydrolysis. One of the most commonly used spacers is the bifunctional p-aminobenzyl alcohol group, which is linked to the peptide through the amine moiety, forming an amide bond.

Furthermore, Dubowchik teaches peptide-DOX (doxorubicin) substrates that contain a self-immolative PABC spacer that are efficiently cleaved by cathepsin B to release free DOX but are very stable in human plasma. Cathepsin B is an attractive target for release of drugs from conjugates that are taken up by receptor-mediated endocytosis since it is ubiquitous and found in relatively high levels in mammalian lysosomes. In addition, several of these compounds release DOX on a time scale that may make them useful as prodrugs for metastatic or primary tumors that express extracellular cathepsin B. Indeed, in view of the teachings of the prior art the instantly claimed conjugates and methods for tumor treatment are obvious.

6. Applicant's arguments filed July 10, 2006 have been fully considered but they are not persuasive. Applicant argues that 1) the combined references do not teach or suggest all the claim limitations, 2) there's no motivation to combine the references and 3) there's no reasonable expectation of success.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208

USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Grissom does not teach away from the instant invention as applicant asserts. Although Grissom teaches that a fluorescent compound may be attached to the corrin ring or the ribose moiety, the passage cited by applicant does not suggest that doxorubicin is not linked to cobalamin via the 5'-OH on the ribose moiety. Although Grissom is silent on the specific attachment of the components of the doxorubicin-cobalamin conjugate, Habberfield teaches that, in general, biologically active conjugates are prepared by reacting the therapeutically active compound with 5'-O-[glutaroyl]cyanocobalamin under conditions which form covalent bonds between the two. Preferably, a 5'-O-glutaroyl derivative of vitamin B12 is formed by acylation of vitamin B12 with a reactive glutaric acid derivative to selectively convert the primary hydroxyl group (5'-OH) on the α-ribose moiety to a chemically reactive carboxyl group. The vitamin B12 derivative is then preferably reacted with a functional linker and/or spacer group to form a second derivative, which in turn is reacted with the therapeutic compound to form a biologically active conjugate. Toki and Dubowchik teach enzyme cleavable linkers/spacers useful for making anti-cancer prodrugs that are activated by cellular enzymes. One of ordinary skill in the art would have been motivated to use an enzyme cleavable linker/spacer in order to make controlled-release anti-cancer compositions. One of ordinary skill in the art at the time of the invention would have had a reasonable expectation of success as Toki teaches,

"This methodology, based on the work of Sartorelli, Katzenellenbogen, and co-workers, has been applied to the plasmin-catalyzed release of phenylenediamine mustard and antracyclines from their corresponding peptide-p-amidobenzyl carbamate derivatives and also to the release of doxorubicin and mitomycin C from peptide-p-amidobenzyl carbamate peptide derivatives by lysosomal enzymes and cathespsin B. The same linkage system has also been applied to the activation of anthracyclines in cells that were transfected with carboxypeptidase G2."

Conclusion

7. Claims 1-21 are pending. Claims 1-21 are rejected. No claims are allowed.

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

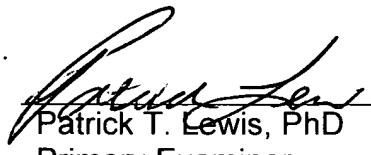
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Contacts

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patrick T. Lewis whose telephone number is 571-272-0655. The examiner can normally be reached on Monday - Friday 10 am to 3 pm (Maxi Flex).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia A. Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Patrick T. Lewis, PhD
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Art Unit 1623

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